EXAMPLE 4

Base Composition Density Distributions for the Total Set of possible 7-base Oligonucleotides

For this implementation, three sets of 7-base oligonucleotides comprising all possible base compositions for a 7-base oligonucleotide can be obtained; the first set comprising the four natural bases (dA, dG, dC and dT), the second set comprising three of the natural bases (dA, dC and dT) and the nucleotide analog 7-deaza-deoxyguanosine (7-deaza-dG) substituted for dG, and the third set comprising three of the natural bases (dA, dG and dC) and the nucleotide analog deutero-deoxythymine (deutero-dT) substituted for dT. Figure 8i-iii shows the actual base composition density distributions for the total set of possible 7-base oligonucleotides using the three different nucleotide sets. Note that for the set of naturally occurring bases (Figure 8i), nearly every base composition has its own distinct mass value, but most of these mass values are spaced only one dalton from each other. Increasing the peak separation to three daltons by substitution of dG with 7-deaza-dG (Figure 8ii) markedly increases the average number of base compositions per observed mass, particularly for those masses in the center of the range, but any two oligonucleotides of the same length with different molecular weights will have to be separated by at least three daltons. Similarly, substitution of dT with deutero-dT (Figure 8iii) gives a minimum peak separation between oligonucleotides having the same length but different molecular weights of eight daltons. The trade-off for a greater peak separation is a greater number of oligonucleotides that have exactly the same mass for a given oligonucleotide length.

IN THE CLAIMS:

Please cancel claim 9 without prejudice or disclaimer.

Please replace claims 4, 8, 17, 24, 36, 39, and 40 with the following amended claims (a marked-up copy of the amended claims is attached to this Amendment):

A12 SubC1

4. (Amended) The method of claim 1, wherein a mass-matched deoxynucleotide is deoxyinosine, 5-nitroindole, 3-nitropyrrole, 3-methyl 7-propynyl isocarbostyril, 5-methyl isocarbostyril or 3-methyl isocarbostyril.

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8. (Amended) The method of claim 5, wherein a mass-matched deoxynucleotide is deoxyinosine, 5-nitroindole, 3-nitropyrrole, 3-methyl 7-propynyl isocarbostyril, 5-methyl isocarbostyril or 3-methyl isocarbostyril.

SubC3 A14

17. (Amended) A method for detecting a one or a plurality of target nucleic acid(s) or one or plurality of nucleotides therein molecules, comprising:

(a) copying the target nucleic acid molecule(s) in the presence of a pair-matched set of nucleotides;

(b) denaturing the resulting copies of the target(s) to produce single-stranded templates;

(c) annealing and ligating one or a plurality of partially duplex hairpin primers to the single-stranded template(s);

(d) extending the primer(s) in the presence of chain terminating nucleotides and pair-matched nucleotides to produce extension products, wherein the extension products follow a periodic mass distribution that is determined by the mass of the pair-matched nucleotide set; and

(e) detecting each of the targets or nucleotides therein by virtue of the mass shift of each extension product from its corresponding periodic reference mass.

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24. (Amended) A kit for determining the sequence of a target nucleic acid, comprising pair-matched nucleotides and mass-labeled primers, and optionally including instructions for sequencing using these reagents.

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36. (Amended) A method for detecting a plurality of target nucleic acid sequences, comprising the steps of:

a) hybridizing a primer or plurality thereof nucleic acid molecules comprising target nucleic acid sequences, wherein the primers can be extended in a 3′ direction towards the target nucleic acid sequence, and

wherein the 5′ end of the hybridized mass-matched nucleic acid molecules can be selectively cleaved from the extension product;

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b) extending the primers in the presence of mass matched deoxyribonucleotides and a polymerase to produce extension products;

c) selectively cleaving the 5′ end of the primers from the extension products to produce portions of the primers and cleaved extension products; and

d) detecting the cleaved extension products.

39. (Amended) The method of claim 38, wherein the cleaved extension product is detected by mass spectrometry.

40. (Amended) A method for detecting a plurality of target nucleic acid sequences, comprising:

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a) hybridizing to each of a plurality of nucleic acid molecules comprising the target nucleic acid sequence

a first primer, which can be extended in a 3′ direction towards the target nucleic acid sequence, and wherein the 5′ end of the primer can be selectively cleaved from the extension product, and

a second primer, which can be extended in a 3′ direction towards the first primer;

b) extending the primers in the presence of mass-matched nucleotides or pair-matched nucleotides to produce double stranded amplification products;

c) selectively cleaving the 5′ end of each of the first primers in the amplification product, to produce double stranded amplification products comprising cleaved primer extension products comprising a 5′ portion and a 3′ portion;

d) denaturing the products of step c); and

e) detecting the 3′ portions of the cleaved primer extension products by virtue of the masses.

REMARKS

Any fees that may be due in connection with filing this paper, or with this application during its entire pendency, may be charged to Deposit Account No. 50—1213.

The specification and the claims are amended to correct obvious typographical, spelling, and formatting errors. The column parameters and values, in the table on page 50 of the specification, are aligned.

Claim 9, which is an identical duplicate of claim 5, is canceled. The claim dependency of claim 8 is corrected to depend from claim 5 defining the mass-matched nucleotide for the independent claim 5.

No new matter has been added.

Entry of this amendment is respectfully requested.

Respectfully submitted,
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